CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo

NDA 22-249
TREANDA®
Date: March 19, 2008

Introduction

TREANDA® (bendamustine HCl) for Injection is a synthetic new molecular entity alkylating agent. It is supplied as a lyophilized powder containing the drug substance (100 mg) and mannitol (170 mg) in 20 mL amber glass vials. At the time of use, the powder is reconstituted with 20 mL Sterile Water for Injection USP to yield a solution of 5 mg/mL bendamustine HCl. This solution is further diluted with normal saline to a concentration of 0.2 to 0.6 mg/mL and administered by IV infusion over 30 minutes.

ONDQA recommends approval.

Administrative

The corresponding IND for this application is 67,554. The NDA was received 19-SEP-2007 was assigned a priority review status (1P) and was part of the GRMP pilot program for Oncology Drug Products. The CMC review was complete as of Feb 27, 2008. At that time, the Environmental Assessment (categorical exclusion justified) and Microbiology reviews (approval recommended) were complete.

However, as per GRMP's the CMC review was completed on the aforementioned date with items NOT under ONDQA control left pending (e.g., EES recommendation). The final recommendation from OC regarding the acceptability of facilities was received 17-MAR-2008 (acceptable overall).

Drug Substance and Drug Product

Bendamustine hydrochloride is a new molecular entity synthetic alkylating agent (nitrogen mustard type). Being a weak base, the solubility in aqueous solvents is pH dependent; being more soluble in acidic media. The drug substance is photosensitive; thus the drug substance is packaged and labeled to be protected from light (

The drug product is a single strength as 100 mg bendamustine HCl plus 170 mg Mannitol, in 20 mL amber glass vials sealed with a rubber stopper topped with a crimped *flip-off* seal. The powder-filled vials are packaged in cardboard containers with the notation to "protect from light" on the side panel of the carton and the notation to "retain in carton until time of use" on the front panel of the carton.

At the time of use, the drug product is reconstituted with with 20 mL Sterile Water for Injection USP to yield a solution of 5 mg/mL bendamustine HCl This solution which is not to be administered may be clear to pale yellow in color.

This is further diluted with normal saline to a concentration of 0.2 to 0.6 mg/mL and administered by IV infusion over 30 minutes. The shelf life of the solution to be infused is three (3) hours at room temperature (including infusion time) or twenty four (24) hours when at 5C.

The lyophilized drug product is stable for 24 months when stored between two (2) and 25 degrees C.

Phase-4 Commitment

The applicant agrees to provide assay and impurity profile data within six (6) months of approval to assess the compatibility and stability of the infusion solution when constituted with other common diluents such as [redacted]

Rik Lostritto, Ph.D., Director
ONDQA, Division-III

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Lostritto
3/19/2008 04:47:27 PM
CHEMIST

CMC Branch Chief Memo

Application: NDA 22-249. Treanda (Bendamustine Hydrochloride) for Injection
Submission type: 505 (b) (1), Type I (NME)
Applicant: Cephalon, Inc., 41 Moores Road, Frazer, PA 19355
Initial Quality Assessment: Sarah Pope, Ph.D. (IQA in DFS dated 10/10/2007)
Primary CMC reviewer: Ravindra Kasliwal, Ph.D. (Review in DFS dated 2/27/2008)

Overall recommendation:

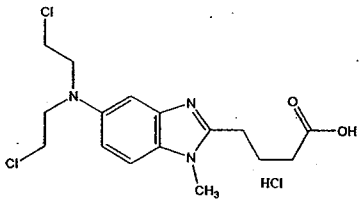
All pending issues subsequent to completion of the primary CMC review have been resolved satisfactorily. The Office of Compliance made an acceptable cGMP recommendation for the NDA on March 17, 2008. The DDMAC and DMETs reviews on labels and labeling were completed and the combined CMC/DMETs comments on labels and labeling were satisfactorily addressed by the firm. An approval recommendation is made for this NDA. A statement on grantable expiration dating period and reminders on a CMC post-marketing commitment and a CMC agreement, listed at the end of this memo, have been included in the action letter.

Background:

The NDA was reviewed under priority clock (6 months) and was the first GRMP pilot in the Division of Drug Oncology Products. The PDUFA date is March 20, 2008.

Introduction:

Bendamustine HCl is a non-sterile, synthetic alkylating agent containing nitrogen mustard structural element and has known genotoxic nature. Chemically, it is 1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl) amino]-1-methyl-, monohydrochloride. The USAN and INN name for the drug substance is bendamustine hydrochloride.The primary CMC review indicated that the long-term drug substance stability data support the proposed — retest period when stored at 2°-25°C (36°-77°F) and protected from light (bendamustine HCl is photosensitive).



$C_{16}H_{22}Cl_3N_3O_2$
Mol. Wt.: 394.7
C, 48.69; H, 5.62; Cl, 26.94; N, 10.65; O, 8.11

The TREANDA® (bendamustine HCl) for Injection is packaged as a lyophilized powder in 20-cc amber glass vials in 100 mg strength. Each 100 mg vial is to be reconstituted

with 20 mL of Sterile Water for Injection (WFI), to yield a 5 mg/mL bendamustine HCl solution. This solution is to be further diluted to a concentration of 0.2 to 0.6 mg/mL with 0.9% Sodium Chloride Injection, USP (NS, normal saline). The product dose is determined based on patient body surface area. The drug product is diluted into 500 mL IV normal saline bags, thus yielding the above drug concentrations. Administration is performed by IV infusion over the recommended 30 minute infusion time. The paperboard folding carton is used to package the vial and is also intended to provide protection from light as bendamustine HCl drug substance is photosensitive (degrades upon exposure to light). The primary CMC review indicates that adequate data are provided to support the requested expiration dating period of 24 month when stored at 2°-25°C (36°-77°F) and retained in the original package to protect from light. The product is required to have the statement "Protect from light" on the label.

Pending CMC-related issues from the primary CMC review:

At the time the primary CMC review was placed in DFS, the following issues were still pending resolution and or feedback.

1. OSE/DMETs review of labels and labeling
2. Overall recommendation from the Office of Compliance
3. CMC post-marketing commitment to include additional studies on compatibility of the drug product with diluents such as
4. Firm's agreement dated 12-Feb-2008 to initiate change controls for all the documents impacted by the revision to the maximum hold time not to exceed C and to submit appropriate post-approval correspondence reflecting this change

The memo serves to address these pending issues and to close out the CMC review and to provide an overall approval recommendation for this NDA.

OSE/DMETs and DDMAC review of labels and labeling:

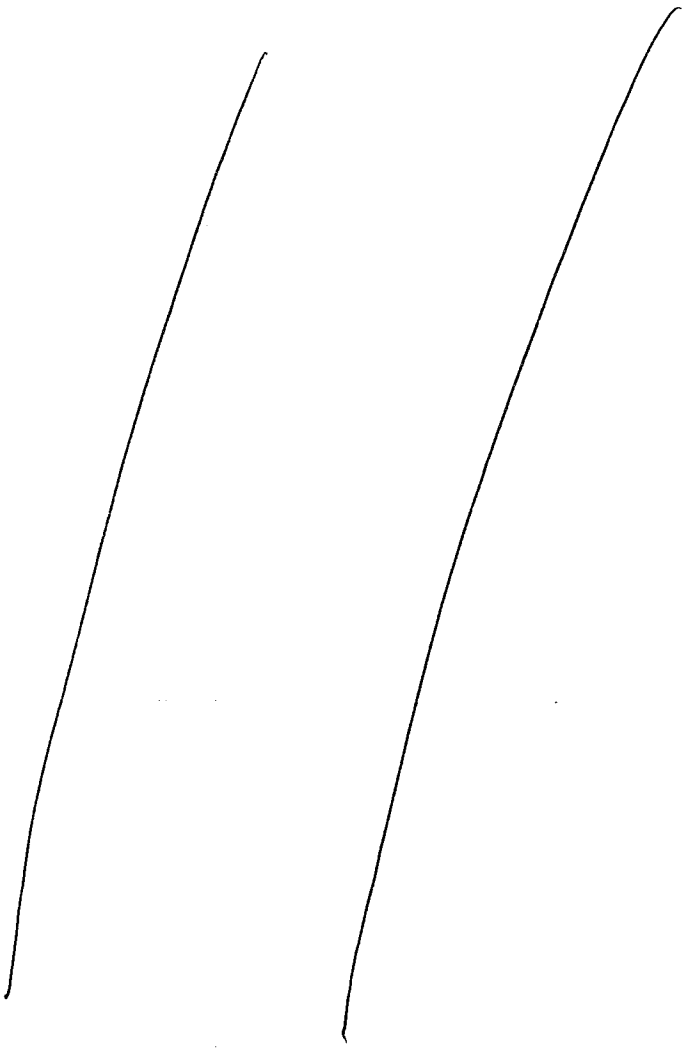
The DDMAC/SEALD review by Iris Masucci was placed in DFS on February 19, 2008. She recommended

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process



The updated package insert was submitted by the firm on March 17, 2008. This was reviewed by the team during the last labeling meeting on March 18, 2008 and was deemed acceptable with some revisions. The final version of the PI is attached (Attachment 3).

Overall recommendation from the Office of Compliance:

On March 17, 2008, the Office of Compliance provided an overall acceptable recommendation for this NDA. The detailed e-mail correspondence is attached (Attachment 1). It can be noted that the [redacted] site, [redacted] was withdrawn from the EES request since this site is only responsible for [redacted] whereas the actual analysis is carried out in the respective manufacturing sites, which are already deemed acceptable. The facility inspection report is attached (Attachment 2). During the initial quality assessment, the pharmaceutical assessment lead entered the sites in EES and indicated that [redacted] was the [redacted] site (profile code CTL). However, during the review it was uncovered that this site only [redacted] was carried out at the drug substance manufacturing site. In retrospect, this site should not have been requested for inspection. This was made clear to me by Edvin Rivera-Martinez. He indicated during a telephone discussion on 3/17/08 that sites such as this, which are meant to [redacted] s, are not routinely inspected unless there is a reason to do so. Therefore, upon discussion with him and as per his recommendation, we withdrew this site from inspection in the EER on 3/17/08.

CMC Post-marketing Commitment and agreement:

The following PMC was agreed to between the Agency and the firm on March 3, 2008. The firm submitted an amendment.

Study title: Assessment of physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: [redacted] sodium chloride)

Protocol submission: April 1, 2008
Study initiation: May 15, 2008
Study report submission: September 1, 2008

Rationale and Background: Treanda admixutre studies were conducted during development using normal saline as the proposed diluent. The study will continue by performing compatibility of the admixture at the end of the proposed shelf life, which is 24 months. Additional commonly used diluents will be added to the end of shelf life study to generate data for alternative diluents. [redacted] Each diluent will be studied over the storage time and temperature in the proposed label.

This commitment was included in the action letter. Similarly, a reminder to the firm, about their agreement to initiate change controls to update the hold times was also included in the action letter.

Attachment 1: E-mail correspondence with the Office of Compliance

From: CDER EESQUESTIONS
Sent: Monday, March 17, 2008 4:18 PM
To: Harapanhalli, Ravi S; Rivera Martinez, Edwin
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Pope, Sarah; Dagher, Ramzi; Cross Jr, Frank H; Kasliwal, Ravindra K; Nasr, Moheb M; Friedman, Rick L; Jones, Carole (OC/DMPQ); Cruz, Concepcion
Subject: RE: NDA 22-249: Treanda. Inspection status of [redacted]

An acceptable overall has been entered into EES.

Shirnette

From: Harapanhalli, Ravi S
Sent: Monday, March 17, 2008 1:38 PM
To: CDER EESQUESTIONS; Rivera Martinez, Edwin
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Pope, Sarah; Dagher, Ramzi; Cross Jr, Frank H; Kasliwal, Ravindra K; Nasr, Moheb M; Friedman, Rick L; Harapanhalli, Ravi S; Jones, Carole (OC/DMPQ); Cruz, Concepcion
Subject: RE: NDA 22-249: Treanda. Inspection status of [redacted]
Importance: High

Edwin,

Thanks for the call and for discussing the pending inspection issue with this NDA. As we discussed, the [redacted] site has been withdrawn from the EES request. This should pave the way for an overall OC recommendation.

When the sites were entered into the EES during the initial quality assessment (IQA) phase of the NDA review, based on the limited information, this site was entered as a stability testing site with a CTL profile code. However, during subsequent in-depth review, we uncovered, this site [redacted] and does not carry out any stability testing. By that time, since the inspections had been scheduled, we communicated with you via the EES Questions e-mail account.

Glad that we could resolve this issue quickly.
Looking forward to an overall compliance recommendation before March 20, 2008.

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment (ONDQA), CDER, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

From: Harapanhalli, Ravi S
Sent: Friday, March 14, 2008 4:06 PM
To: Jones, Carole (OC/DMPQ); Cruz, Concepcion; CDER EESQUESTIONS
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Pope, Sarah; Dagher, Ramzi; Cross Jr, Frank H; Kasliwal, Ravindra K; Nasr, Moheb M; Rivera Martinez, Edwin; Friedman, Rick L
Subject: RE: NDA 22-249: Treanda. Inspection status of [redacted]
Importance: High

Your e-mail indicates that the facility. [redacted] cannot

be inspected until after the PDUFA date. However, as indicated earlier, the NDA is being recommended for approval from all the disciplines and the Medical Division is looking forward to the action and to meet the PDUFA goal date, which is March 20, 2008. Also, pending the — site, all other facilities have been deemed acceptable for cGMPs.

It appears that there is a case for regulatory discretion to waive the inspection of and to approve the NDA. The facility may then be inspected following the approval of the NDA, as scheduled on April 7-8, 2008. Here are the reasons.

1. — is the facility for —— . This facility **does not** analyze the stability samples.

2. The stability samples are analyzed by the respective drug substance and the drug product manufacturing sites, which have already been inspected and deemed acceptable for cGMP compliance.

3. Analysis of primary and supporting stability data provided in the NDA indicates that the drug substance and the drug product are stable over a wide temperature range from 2 C to 40 C. There were no significant changes on accelerated storage at 40C/75% RH over — Therefore, it is a very stable drug.

Understandably, — is a new facility and has never been inspected. However, given that the product is stable over a wide range of temperatures and any temperature fluctuations in the stability chambers may not significantly affect the product quality, we recommend a risk based approach in the regulatory discretion to provide an overall recommendation now and to conduct the inspection of this facility as scheduled. This will assure that the PDUFA date can be met for this priority NDA, which was reviewed under GRMP pilot program.

If you have any questions, please let us know.

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment (ONDQA), CDER, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

From: Jones, Carole (OC/DMPQ)
Sent: Wednesday, March 12, 2008 4:02 PM
To: Harapanhalli, Ravi S; Cross Jr, Frank H; Kasliwal, Ravindra K; Cruz, Concepcion
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Pope, Sarah; Dagher, Ramzi
Subject: RE: NDA 22-249: Treanda. Inspection status of —

Unfortunately, the inspection could not be planned prior to the PDUFA date. It is schedule fo — Since this is a new facility with no previous GMP history, we cannot provide a GMP assessment of this facility at this time.

Thanks,
Carole Jones
Acting Team Leader

International Compliance Team
301-796-3194

From: Harapanhalli, Ravi S
Sent: Wednesday, March 12, 2008 3:56 PM
To: Cross Jr, Frank H; Kasliwal, Ravindra K; Jones, Carole (OC/DMPQ); Cruz, Concepcion
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Pope, Sarah; Dagher, Ramzi
Subject: RE: NDA 22-249: Treanda. Inspection status of '

Let us wait to hear back from OC.

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment (ONDQA), CDER, FDA,
Bldg. 22, Room #.2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

From: Cross Jr, Frank H
Sent: Wednesday, March 12, 2008 3:55 PM
To: Kasliwal, Ravindra K; Harapanhalli, Ravi S; Jones, Carole (OC/DMPQ); Cruz, Concepcion
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Pope, Sarah; Dagher, Ramzi
Subject: RE: NDA 22-249: Treanda. Inspection status of

So we are going to miss the PDUFA Date.

Frank

From: Kasliwal, Ravindra K
Sent: Wednesday, March 12, 2008 3:51 PM
To: Cross Jr, Frank H; Harapanhalli, Ravi S; Jones, Carole (OC/DMPQ); Cruz, Concepcion
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Pope, Sarah
Subject: RE: NDA 22-249: Treanda. Inspection status of

Frank,

This is the only site and there is no alternate site for the task . So the site is required for approval. Obviously they could not find the profile.

Ravi Kasliwal

From: Cross Jr, Frank H
Sent: Wednesday, March 12, 2008 3:38 PM

To: Harapanhalli, Ravi S; Jones, Carole (OC/DMPQ); Cruz, Concepcion
Cc: Lostritto, Richard T; Justice, Robert; Ibrahim, Amna; Kasliwal, Ravindra K; Pope, Sarah
Subject: RE: NDA 22-249: Treanda. Inspection status of [redacted]

Is this site required for approval?

If so, can this be a profile.

Thanks,
Frank

From: Harapanhalli, Ravi S
Sent: Wednesday, March 12, 2008 3:32 PM
To: Jones, Carole (OC/DMPQ); Cruz, Concepcion
Cc: Harapanhalli, Ravi S; Lostritto, Richard T; Cross Jr, Frank H; Justice, Robert; Ibrahim, Amna; Kasliwal, Ravindra K; Pope, Sarah
Subject: RE: NDA 22-249: Treanda. Inspection status of [redacted]
Importance: High

Please note that the PDUFA date is March 20, 2008 (not March 30 as indicated in your e-mail below) and the Division intends to take an early action if possible. If the inspection of [redacted] is scheduled on [redacted] we won't be able to meet the PDUFA date.

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment (ONDQA), CDER, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

From: Jones, Carole (OC/DMPQ)
Sent: Wednesday, March 12, 2008 2:37 PM
To: Cruz, Concepcion; Harapanhalli, Ravi S
Subject: FW: Inspection status of [redacted]

Please see Irma's e-mail below for the inspection date of [redacted]

Thanks,
Carole Jones
Compliance Officer
FDA/CDER/OC/DMPQ
International Compliance Team
301-796-3194

From: Rivera, Irma

Sent: Tuesday, March 04, 2008 9:02 AM
To: Hackett, Rebecca R; Adams. Shawnte L
Subject: RE: Inspection status of

This inspection is scheduled for

From: Adams, Shawnte L
Sent: Tuesday, February 26, 2008 10:51 AM
To: Hackett, Rebecca R
Subject: Inspection status of

Becky,

Please provide the status of the inspection scheduling of
This facility is listed in NDA 22249 which has a PDUFA date of March 30, 2008.

Thank you,

Shawnte L. Adams
Program Analyst
Office of Compliance
Division of Manufacturing and Product Quality
International Compliance Team
301-796-3193 (Office)

General Foreign Inspection questions should be directed to:
cderict@fda.hhs.gov
FWAP: Tuesday and Thursday

ESTABLISHMENT EVALUATION REQUEST

SUMMAY REPORT

Application NDA 22249/000 Sponsor: CEPHALON INC
Org Code150 NO CITY, , XX
Priori ty 1P

Brand Name : TREANDA

Stamp Date 20-SEP-2007 Estab. Name:
PDUFA Date 20-MA-2008 Generic Name: BENDAMUSTINE HCL

Action Goal Dosage Form: (INJECTION)
District Goal: 20 -JAN-2008 Strength 100 MG/VIAL

FDA Contacts: K. STILLER Project Manager (HFD-580) 301796 1993
R. KASLIWAL Review Chemist 301-796-1386
R. HARAPANHALLI Team Leader 301-796-1676

Overall Recommendation: ACCEPTABLE on 17-MAR-2008 by C. CRUZ (HFD-323) 301-796-3254

Establishment : CFN : [redacted] FEI :

[redacted]

DMF No: AAA:

Responsibilities: [redacted]

Profile CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-FEB-08
Decision ACCEPTABLE
Reason DISTRICT RECOMMENDATION

Establishment : CFN [redacted] FEI [redacted]

[redacted]

DMF No: —

Responsibilities:

Profile SVL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-NOV-07
Decision ACCEPTABLE
Reason DISTRICT RECOMMENDATION

Establishment : CFN — FEI —

IS-MA-200S

DMF No:

Responsibilities: Profile

Last Milestone:
Milestone Date:

Decision
Reason

Establishment :

DMF No:

Responsibilities: Profile

Last Milestone:
Milestone Date:

Decision
Reason

OAI Status: NONE

SVL OC RECOMMENDATION 15-0CT-07 ACCEPTABLE DISTRICT RECOMMENDATION

CFN :

FEI :

OAI Status: NONE

SVL OC RECOMMENDATION 01-0CT-07 ACCEPTABLE BASED ON PROFILE

Attachment 3: Final package insert dated 3/18/2008: (This is the revised version based on the labeling meeting at 2:30 PM on 3/18/08)

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ON ORIGINAL

16 Page(s) Withheld

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/ Draft Labeling

_____ Deliberative Process

Label Code: PI-40014-00

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March 14 2008 Ceph Version
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CMC comments and reminders to be included in the action letter:

1. An expiration dating period of 24 months is granted when stored as recommended in the approved product labeling. You may extend the expiration dating based on accrual of real-time stability data and report this in an annual report for this NDA.
2. Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: [redacted] sodium chloride).

   Protocol submission: April 1, 2008
   Study start: May 15, 2008
   Final Report: September 1, 2008
3. We also remind you of your agreement dated 12-Feb-2008 to initiate change controls for all the documents impacted by the revision to the maximum hold time not to exceed [redacted] and to submit appropriate post-approval correspondence reflecting this change in the next annual report.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ravi Harapanhalli
3/19/2008 09:49:56 AM
CHEMIST
AP recommendation

Richard Lostritto
3/19/2008 11:16:59 AM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22249/000
Org Code : 150
Priority : 1P

Sponsor: CEPHALON INC
NO CITY, , XX

Stamp Date : 20-SEP-2007
PDUFA Date : 20-MAR-2008
Action Goal :
District Goal: 20-JAN-2008

Brand Name : TREANDA
Estab. Name:
Generic Name: BENDAMUSTINE HCL
Dosage Form: (INJECTION)
Strength : 100 MG/VIAL

FDA Contacts:			
	K. STILLER	Project Manager (HFD-580)	301-796-1993
	R. KASLIWAL	Review Chemist	301-796-1386
	R. HARAPANHALLI	Team Leader	301-796-1676

Overall Recommendation: ACCEPTABLE on 17-MAR-2008by C. CRUZ (HFD-323) 301-796-3254

Establishment : CFN [redacted] FEI :

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-FEB-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
OAI Status: NONE

Establishment : CFN : [redacted] FEI :

DMF No: AADA:

Responsibilities:

Profile : SVL
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-NOV-07
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
OAI Status: NONE

Establishment : CFN : [redacted] FEI : [redacted]

DMF No:

AADA:

Responsibilities:

Profile : SVL
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-OCT-07
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

OAI Status: NONE

Establishment : CFN : FEI :

DMF No:

AADA:

Responsibilities:

Profile : SVL
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-OCT-07
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

OAI Status: NONE

NDA 22-249

TREANDA®
(bendamustine hydrochloride) for injection

Cephalon, Inc.
41 Moores, Rd.
Frazer, PA 19355

Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Division of Pre-marketing Assessment and Manufacturing Science,
Branch V, ONDQA
CDER, FDA

For The Division of Drug Oncology Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 22-249**
2. REVIEW #: 1
3. REVIEW DATE: 19-Feb-2008 (revised 27-Feb-2008)
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	19-Sep-2007
Amendment (BC)	17-Dec-2007
Amendment (BC)	12-Feb-2008
Amendment (BC)	14-Feb-2008
Amendment (BC)	22-Feb-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Cephalon, Inc.
Address:	41 Moores Road, P.O. Box 4011, Frazer, PA 19355
Representative:	Carol S. Marchione, Sr. Director and Group Leader, Regulatory Affairs
Telephone:	(610) 738-6237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Treanda®
b) Non-Proprietary Name: Bendamustine hydrochloride (USAN & INN)
c) Code Name/# (ONDC only): CEP-18083, BM1, SDX-105, ID08736, M008736, ID00275, M000275, ID00039, M000039, IMET 3393, ZIMET 3393
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b) 1 application.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Alkylating Agent

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 100 mg/vial

13. ROUTE OF ADMINISTRATION: intravenous

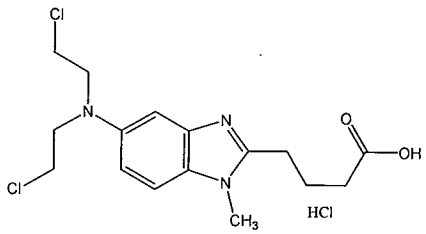
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 1H-Benzimidazole-2-butanoic acid, 5-[bis (2-chloroethyl) amino]-1-methyl-, monohydrochloride



$C_{16}H_{22}Cl_3N_3O_2$
Mol. Wt.: 394.7
C, 48.69; H, 5.62; Cl, 26.94; N, 10.65; O, 8.11

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	III	/	/	3, 4	Adequate	22-Apr-2002 by Yvonne Yang, Ph.D	None
/	III	/	/	3, 4	Adequate	10-Oct-2002 by Dr. Elsbeth Chikale	None

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cephalon IND for bendamustine HCl	IND 67, 554	N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Analytical methods are conventional; DPA verification will not be requested.		
OSE / DMETS	PENDING	Pending	
EA	Claim for categorical exclusion is justified	Same as the review date.	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	06-Feb-2008	Anastasia G. Lolas

The Chemistry Review for A/NDA 22-249

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided trademark and labeling acceptability has been determined by Office of Drug Safety (DMETS) and provided the manufacturing sites are deemed acceptable for cGMP compliance. The product quality microbiology has recommended approval on 06-Feb-2008. The recommendation for Office of Compliance regarding the acceptability of the manufacturing facilities is pending as of the date of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The company has not provided data showing compatibility of the constitution solution, Sterile Water for Injection, USP, with other commonly available diluents such as [redacted] The data (assay and impurity profile) should be provided as part of the phase 4 commitment within 6 months of approval of the application (comment for company is provided at the end of this review).

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The TREANDA® (bendamustine HCl) for Injection is packaged as a lyophilized powder in 20-cc amber glass vials in 100 mg strength. Each 100 mg vial is to be reconstituted with 20 mL of Sterile Water for Injection (WFI), to yield a 5 mg/mL bendamustine HCl solution. This solution is to be further diluted to a concentration of 0.2 to 0.6 mg/mL with 0.9% Sodium Chloride Injection, USP (NS, normal saline). The product dose is determined based on patient body surface area. The drug product is diluted into 500 mL IV normal saline bags, thus yielding the above drug concentrations. Administration is performed by IV infusion over the recommended 30 minute infusion time. The paperboard folding carton is used to package the vial and is also intended to provide protection from light as bendamustine HCl drug substance is photosensitive (degrades upon exposure to light).

TREANDA® contains a new chemical entity, (1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl) amino]-1-methyl-, monohydrochloride). The USAN and INN name for the drug substance is bendamustine hydrochloride. It has a molecular weight of 394.7. The aqueous solubility of bendamustine hydrochloride is dependent on pH. The aqueous solubility at 20°C, at pH 1.9 is [redacted] mg/mL, at pH 3.3 is [redacted] mg/mL and at pH 4.1 is [redacted] mg/mL. The solubility of the drug product, bendamustine HCl for injection was determined by HPLC assay to be [redacted] mg/mL in water and [redacted] g/mL in 0.9% sodium chloride for injection (saline). [redacted] The 1-octanol/water partition coefficient (log $P_{o/w}$) of [redacted] at pH 7.4 is [redacted]

Bendamustine hydrochloride drug substance will be manufactured at the [redacted] The commercial manufacture involves [redacted]

[redacted] . Bendamustine HCl is a [redacted] synthetic alkylating agent containing nitrogen mustard structural element and has known genotoxic nature. Various starting material, process

reagents and intermediates used in the manufacture are considered genotoxic alerts due to their structure. Bendamustine HCl is administered as an intravenous injection. Based on the anticipated dosing schedule, the total use of this drug product is less than 30 days (doses) of administration. The daily dose of bendamustine HCl is not expected to exceed 200 mg. The potential maximum structural alert dose can therefore be calculated as 200 mg times the limit of detection, and ranges from dose. The company was told of the control of genotoxic alerts in the pre-NDA meetings. These amounts are higher than generally recommended limit of g/day. Considering that the drug substance itself is carcinogenic / mutagenic the company's approach to controlling these potential structural alerts is acceptable, as it does not have impact on product risk assessment. The other specified impurities are controlled at limits for which justifications are provided.

Adequate CMC information has been provided for the manufacture and control of bendamustine HCl drug substance. The long-term drug substance stability data support the proposed retest period when stored at 2°-25°C (36°-77°F) and protected from light (bendamustine HCl is photosensitive).

TREANDA® (bendamustine HCl) for Iniection vials will be manufactured at

TREANDA® for injection will be supplied in 100 mg strength and is a single-use, sterile, lyophilized powder for intravenous (IV) infusion following constitution with 20 mL of Sterile Water for Injection (WFI) and further dilution with 0.9% Sodium Chloride Injection, USP. TREANDA® (bendamustine HCl) for Injection vial only contains 170 mg mannitol as excipient along with 100 mg lyophilized bendamustine HCl drug substance. The product is manufactured by

t. The commercial packaging for bendamustine HCl for Injection (100 mg/vial) is a 20cc amber glass tubing vial. The vials are stoppered with a 20-mm stopper and sealed with a flip-off crimp seal. Each sealed vial is packaged in a olding carton to provide light protection. The suitability of the packaging system for commercialization has been demonstrated by the stability studies.

Adequate CMC information has been provided for the manufacture and control of TREANDA® for injection. Adequate data are provided to support the requested expiration dating period of 24 month when stored at 2°-25°C (36°-77°F) and retained in the original package to protect from light. The product is required to have the statement "Protect from light" on the label.

B. Description of How the Drug Product is Intended to be Used

TREANDA, reconstituted and diluted, product is intended for intravenous infusion over a 30-minute period.

The TREANDA (bendamustine HCl) for injection is reconstituted with 20 mL of Sterile Water for Injection (WFI), to yield a 5 mg/mL bendamustine HCl solution. The reconstituted solution is clear, colorless to pale yellow in appearance. The reconstituted TREANDA solution should be used (i.e. further diluted with 0.9% Sodium chloride Injection, USP) immediately (within 30 minutes) and should be stored in the original vial during this period. Based on bendamustine assay, the reconstituted solution in the glass vial may be stored up to . Use time in the vial is, however, restricted to 30-minutes, so that infusion hold time in the IV bag can be maximized.

Prior to intravenous (IV) administration the constituted solution must be further diluted with 0.9% Sodium chloride Injection, USP in a 500 mL IV bag, to a final concentration between 0.2 mg/mL and 0.6 mg/mL. The solubility of the drug product, bendamustine HCl for injection was determined by HPLC assay to be ng/mL in water and mg/mL in 0.9% sodium chloride for injection (saline). The label instructions for preparation of bendamustine HCl for injection indicate that a 100 mg drug product vial is to be reconstituted with 20 mL of sterile water for injection (SWFI) and then the appropriate volume of reconstituted solution needed for the dose is added to a 500 mL IV bag of 0.9% sodium chloride solution for administration to a patient. The patient dose when diluted in a 500 mL 0.9% Sodium chloride Injection in IV bag yields the above concentrations. Only water for injection, USP must be used for reconstituting the vial and 0.9% Sodium chloride Injection for preparation of the infusion solution. Compatibility with other solutions has not been evaluated. The bendamustine HCl solution in 0.9% Sodium chloride Injection,

USP has a shelf life of 3 hours at room temperature and room light, or 24 hours at 5°C. The infusion should be completed within this 3-hour period at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The approval recommendation is pending provided that, (1) acceptable cGMP recommendation on manufacturing facility is received from the CDER Office of Compliance , and (2) pending acceptability of trademark and labeling by DMETS.

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D. (signed in DFS)

B. Endorsement Block

Ravindra K. Kasliwal/Date: Dee DFS
Ravi S. Harapanhalli/Date: See DFS
Dorothy Pease/Date: See DFS

C. CC Block – See DFS

104 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ravi Kasliwal
2/27/2008 02:42:12 PM
CHEMIST

Ravi Harapanhalli
2/27/2008 04:28:09 PM
CHEMIST

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	22-249
Applicant:	Cephalon
Stamp date:	21-SEP-2007
PDUFA Date:	21-MAR-2008 (designated priority; GRMP pilot)
Proposed Trade Name:	Treanda
Established Name:	Bendamustine hydrochloride for injection
Laboratory Code:	N/A
Dosage Form:	Lyophilized powder
Route of Administration:	Intravenous injection
Indication:	Treatment of chronic lymphocytic leukemia.

Pharmaceutical Assessment Lead: Sarah C. Pope, Ph.D.

	YES	NO
ONDQA Fileability:	√	
Draft Comments for 74-Day Letter:		√

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-249 is submitted for Treanda (bendamustine hydrochloride for injection), 100 mg/vial, intended for treatment of chronic lymphocytic leukemia. Bendamustine hydrochloride is a new molecular entity.

Bendamustine hydrochloride was studied under IND 67,554, which has been active at the Agency since 02-JUN-2003. A CMC-specific EOP2 meeting was held on 09-MAY-2005, and an additional CMC-specific (Type B) meeting was held on 10-OCT-2006. Official meeting minutes are filed under IND 67,554.

Drug Substance Summary

Bendamustine hydrochloride is a white to off-white powder which is very soluble in both methanol and ethanol, and less soluble in more nonpolar solvents (acetone, ethyl acetate, acetonitrile). Bendamustine hydrochloride possesses a maximal aqueous solubility at a pH of — mg/mL); aqueous solubility decreases with increases in pH. A full solubility profile is detailed in the NDA submission. The structure of the bendamustine free base is represented below (Figure 1).

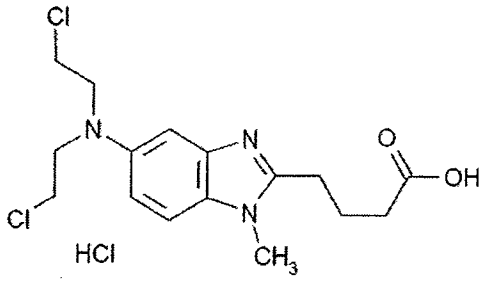


Figure 1. Bendamustine (MW=394.7 g/mole)

The Applicant proposes the following manufacturing site for the manufacture, packaging, testing, and labeling of bendamustine hydrochloride:

Bendamustine hydrochloride is manufactured via a conventional chemical synthesis, —

Once manufactured, bendamustine hydrochloride is tested for conformance to the following specifications:

The Applicant provides stability data for three batches (two half-scale and one full-scale) of the drug substance manufactured using the proposed commercial process. [redacted] months of real time data are provided under storage conditions of 25°C/60% RH, and [redacted] months of stability data are provided under storage conditions of 5°C/ambient humidity conditions. The Applicant also includes photostability, accelerated and supportive stability data for the drug substance; the applicability of these data will be determined during the CMC review process.

The Applicant proposes a [redacted] retest date for the drug substance, when stored between 2°C and 25°C.

Drug Product Summary

Bendamustine hydrochloride for injection is formulated as non-pyrogenic, lyophilized powder (100 mg/vial) for reconstitution and intravenous administration. The formulation includes the API and mannitol. [redacted] are also used in manufacture, but are removed during processing.

The Applicant outlines two formulations in the current submission. The first formulation included [redacted] and was used to support a chronic lymphocytic leukemia indication (Study 02CLLIII, Study SDX-105-01, Study SDX-105-02) in patients with non-Hodgkins lymphoma. The subsequent [redacted] The modified formulation was used in the Phase 3 pivotal trial (Study SDX-105-03) and is intended for commercial production.

The proposed primary manufacturing site is listed below:

[redacted]

Bendamustine hydrochloride for injection is manufactured by [redacted] The final drug product is tested for [redacted] The constituted solution is tested for conformance with specifications for completeness and clarity of solution, particulate matter, and reconstitution time. Bendamustine hydrochloride for injection is packaged into 20-cc glass tubing vials stoppered with a [redacted] stopper and sealed with a flip-off crimp seal. Each sealed vial is packaged into a [redacted] folding carton for light protection.

The Applicant provides [redacted] months of long term (5°C ± 3°C and 25°C/60% RH) stability data for three exhibit batches of bendamustine hydrochloride for injection, when stored in both upright and inverted positions. Photostability conditions were studied using one of the primary stability batches. Supportive and accelerated data are also provided; the applicability of these supportive data will be determined during the CMC review.

The Applicant proposes a 24-month expiration dating period for the drug product, when stored at up to 25°C with excursions permitted to 30°C and protected from light.

B. Critical issues for review and recommendation

Drug Substance

a. The Applicant provides both primary and supportive stability data for the drug substance. The applicability of the provided supportive data should be confirmed as soon as possible during the CMC review process. According to the principles stated in current GRMP guidelines (a complete application is to be provided at the date of submission) and given the short review timeline expected, the retest date approved as part of this application will be determined based on data provided at the time of original NDA submission.

b. The acceptability of the Applicant's proposed starting material should be confirmed.

Drug Product

a. The Applicant provides both primary and supportive stability data for the drug product. The applicability of the provided supportive data should be confirmed as soon as possible during the CMC review process. According to the principles stated in current GRMP guidelines (a complete application is to be provided at the date of submission) and given the short review timeline expected, the expiration dating period approved as part of this application will be determined based on data provided at the time of original NDA submission.

b. The Applicant outlines two formulations used during development. Adequate bridging of these formulations (if required) should be confirmed as part of the CMC review.

c. The sterility assurance portion of this NDA has already been consulted to the Office of Microbiology. In order to recommend an approval for this NDA, a recommendation for approval from the Office of Microbiology needs to be received.

C. Comments for 74-day Letter:

None

D. Recommendation for fileability: Fileable

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items have already been completed)	√ √ √ √		**Microbiology** Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMETS/ODS (clin PM) **EER**

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
[redacted]			Yes
[redacted]			Yes

Recommendation for Team Review:

Due to the anticipated priority review of this application and the probable accelerated review timeframes, the team approach is not recommended for this NDA.

Sarah C. Pope, Ph.D.
Pharmaceutical Assessment Lead

01-OCT-2007
Date

Ravi Harapanhalli, Ph.D.
Branch Chief

01-OCT-2007
Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sarah Pope
10/10/2007 10:28:09 AM
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Ravi Harapanhalli
10/10/2007 03:51:40 PM
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